Remarks

Reconsideration of this Application is respectfully requested.

The foregoing amendments are believed to place the claims in condition for allowance or in better condition for consideration on appeal. No new claims have been added. Various claims have been amended or canceled. The amendments do not present new issues or require additional search. 37 C.F.R. § 1.116(a). Accordingly, their entry after final rejection is respectfully requested.

I. Status of the Claims

Claims 30-34, 65-68, 73, 74, 82-95, 186, 188-190, 195, and 206-212 are pending in the application, with claims 30, 31, 65, and 186 being the independent claims.

Claims 1-29, 35-64, 69-72, 75-81, 96-185, 187, 191-194, 196-205, and 213-286 have been deleted solely to expedite prosecution of the elected method claims. Applicants reserve the right to pursue the cancelled subject matter in one or more continuing applications.

Claims 30, 31, 65, and 186 have been amended to recite "other than the Golgi resident polypeptide that provides the glycosyltransferase activity of said fusion polypeptide." Support for this amendment can be found at paragraphs [0104], [0016], and [0018] of the specification as filed. Claim 186 has been amended to correct a minor informality.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. The Rejections

A. Rejections Under 35 U.S.C. § 102(b)

Claims 30-34, 65-67, 73, 74, 82-95, 186, 188, 189, 195, and 206-212 are rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by PCT publication WO 99/54342 ("Umaña *et al.*") as evidenced by Grabenhorst *et al. J. Biol. Chem. 274*:36107-36116 (1999) ("Grabenhorst *et al.*") and Shields *et al. J. Biol. Chem. 277*:26733-26740 (2002) ("Shields *et al.*"). Applicants respectfully traverse these rejections.

In rejecting claims 30-34, 65-67, 73, 74, 82-95, 186, 188, 189, 195, and 206-212, the Examiner asserts that Umaña *et al.* teaches "mammalian cell lines (i.e. CHO hamster cells) modified to express the GnT III enzyme as a fusion protein with various tags, such as GFP or myc-tags, along with various IgG molecules." (Office Action at page 3). Applicants respectfully disagree with the Examiner's rejection as it is applied to the amended claims.

A claim is anticipated only if each and every element as set forth in the claim is either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic v. Genentech, Inc.,* 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991).

Applicants have amended independent claims 30, 31, 65, and 186 so that they recite "comprises the Golgi localization domain of a Golgi resident polypeptide ***other than*** the Golgi resident polypeptide that provides the glycosyltransferase activity of said fusion polypeptide." (emphasis added) Umaña *et al.* discusses the use of glycosyltransferases fused with various protein tags, but does not teach the use of mammalian host cells expressing a fusion polypeptide comprising (i) β(1,4)-N-acetylglucosaminyltransferase III (GnT III) activity or β(1,4)-galactosyltransferase (GalT) activity and (ii) the Golgi localization domain of a Golgi resident polypeptide ***other than*** the Golgi resident polypeptide that provides the glycosyltransferase activity of said fusion polypeptide. As such, Applicants respectfully submit that Umaña *et al.* does not teach each and every limitation of amended claims 30, 31, 65, and 186. Accordingly, Umaña *et al.* does not anticipate amended claims 30, 31, 65, and 186. It follows that Umaña *et al.* does not anticipate any of the claims that are dependent from amended claims 30, 31, 65, and 186, including pending claims 32-34, 66-68, 73-74, 82-95, 188-190, 195, and 206-212.

In rejecting claim 67, the Examiner asserts that "the rat GntIII (page 26) used by Umana et al is considered to comprise a heterologous Golgi localization domain relative to the hamster CHO cell lines." (Office Action at page 3). Claim 67 depends from independent claim 65. As discussed above, Umaña *et al.* does not anticipate independent claim 65 as amended and, therefore, does not anticipate dependent claim 67.

In rejecting claims 92-95 and 209-212, the Examiner asserts that "the results of Umana et al indicate that up to 45-50% of the glycans are bisected, non-fucosylated upon expression of GnT-III (page 37, and Figures 9-10)." (Office Action at page 4, lines 12-

14). Claims 92-95 depend either directly or indirectly from independent claim 65 and claims 209-212 depend either directly or indirectly from independent claim 186. As discussed above, Umaña *et al.* does not anticipate independent claims 65 and 186 as amended and, therefore, does not anticipate dependent claims 92-95 and 209-212.

In rejecting claim 83, the Examiner asserts that "the instant specification (¶ [0031] of the published application) teaches FcγRIIIA to be an activating receptor." (Office Action at page 4, lines 15-16). Claim 83 depends from claim 82 which in turn depends from independent claim 65. As discussed above, Umaña *et al.* does not anticipate independent claim 65 as amended and, therefore, does not anticipate dependent claim 83.

In rejecting claim 186, the Examiner asserts that "Umana et al teach that the cells of their invention may also comprise mannosidase II, or Man II, which may be expressed with GnTIII (pages 7 and 13)." (Office Action at page 4, lines 17-18). Applicants submit that Umaña *et al.* does not each and every limitation of amended claim 186 as Umaña *et al.* does not teach the use of mammalian host cells co-expressing a polypeptide having Man II activity with a fusion polypeptide comprising (i) GnT III activity and (ii) the Golgi localization domain of a Golgi resident polypeptide ***other than*** the Golgi resident polypeptide that provides the glycosyltransferase activity of said fusion polypeptide. Accordingly, Umaña *et al.* does not anticipate claim 186.

In view of the above, it is respectfully requested that the rejections of claims 30-34, 65-67, 73, 74, 82-95, 186, 188, 189, 195, and 206-212 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

B. Rejections Under 35 U.S.C. § 103(a)

Claims 68 and 190 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Umaña *et al.* as evidenced by Grabenhorst *et al.* and Shields *et al.* in view of PCT publication WO 01/29242 A2 ("Russell *et al.*") and Rabouille *et al. J. Cell. Sci. 108*:1617-1627 (1995) ("Rabouille *et al.*"). Applicants respectfully traverse these rejections.

In order to establish a *prima facie* case of obviousness, (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) there must be some reason, either in the references themselves or in the knowledge generally available to one of ordinary skill the art, to modify the reference or to combine reference teachings; and (3) there must be a reasonable expectation of success. M.P.E.P. § 2143. The Examiner has the burden of establishing a *prima facie* case of obviousness.

1. Umaña et al.

As discussed above, Umaña *et al.* does not teach the use of host cells expressing a fusion polypeptide comprising (i) GnT III or GalT activity and (ii) the Golgi localization domain of a Golgi resident polypeptide ***other than*** the Golgi resident polypeptide that provides the glycosyltransferase activity of said fusion polypeptide. Nor does Umaña *et al.* teach the use of mammalian host cells expressing glycosyltransferases comprising (i) GnT III or GalT activity and (ii) the Golgi localization domains of glycosyltransferases that normally reside in the ***medial*** Golgi (*i.e.,* Man II or β(1,2)-N-acetylglucosaminyltransferase II (GnT II)).

The Examiner asserts that "Umana et al suggest that in order to improve the glycosylation pattern of antibodies for increased ADCC, it would be desirable to re-

distribute the GalT enzyme by exchanging its transmembrane domain (i.e. its localization domain) with that of another enzyme found in the trans Golgi network, e.g. α2,6-sialyltransferase, such that GalT would be further removed from competition with GnTIII for substrates." (Office Action at page 5). Contrary to the Examiner's assertion, Applicants submit that Umaña *et al.* only indicates that it ***might*** be desirable to redistribute the GalT glycosyltransferase towards the TGN instead of the *trans*-Golgi cisterna ***if*** it is determined that galactosylated, bisected complex bi-antennary oligosaccharides are the optimal structures for increased ADCC activity. Even assuming, *arguendo*, that Umaña *et al.* suggests redistributing GalT to the *trans*-Golgi network, Umaña *et al.* certainly does not teach or suggest redistributing GalT to the ***medial*** Golgi where Man II and GnT II reside. As such, Umaña *et al.* does not teach or suggest all the claim limitations of claim 68 or claim 190.

2. Grabenhorst et al.

Grabenhorst *et al.* describes fusion glycosyltransferases having human α(1,3)-fucosyltransferase VI (FT6) catalytic activity and the Golgi localization domain of glycosyltransferases that normally reside either in the ***trans***-Golgi cisterna or in the TGN (*i.e.*, GnT I, GnT III, GalT, ST3, ST4, ST6, PST, FT3, and FT7). Grabenhorst *et al.* does not teach redistributing FT6 to the ***medial*** Golgi where Man II and GnT II reside, much less the redistribution of GalT or GnT III to the medial Golgi. Accordingly, Grabenhorst *et al.* fails to teach or suggest all the claim limitations of claim 68 or claim 190. Grabenhorst *et al.* does not cure the deficiencies of Umaña *et al.* Further, there is no suggestion or motivation to use a host cell expressing a fusion polypeptide comprising (i) GnT III or Gal T activity and (ii) the Golgi localization domain of Man II simply by

combining Umaña *et al.* and Grabenhorst *et al.* either in the references or in the art. Additionally, the references combined fail to provide a reasonable expectation for successfully generating the particular glycoengineered whole antibody molecules, antibody fragments, or fusion proteins that include a region equivalent to the Fc region of an immunoglobulin produced by the methods of claims 68 and 190.

3. Shields et al.

Shields *et al.* discusses the expression of the anti-HER Hu4D5 antibody in a variant CHO cell line, wherein the expressed antibody has increased Fc receptor binding affinity and ADCC activity. However, Shields *et al.* does not discuss the redistribution of glycosyltransferases, much less the redistribution of GnT III or GalT. As such, Shields *et al.* also does not cure the deficiencies of Umaña *et al.* The combination of Umaña *et al.,* Grabenhorst *et al.,* and Shields *et al.,* also fails to provide a reasonable expectation for successfully generating the particular glycoengineered whole antibody molecules, antibody fragments, or fusion proteins that include a region equivalent to the Fc region of an immunoglobulin produced by the methods of claims 68 and 190.

4. Russell et al.

The Examiner states that

> Russell et al disclose that post-translational modification enzymes includes the general use of N-acetylglucosaminyltransferases (page 8, last ¶). CMS regions to be used are from enzymes that prepare the glycans for subsequent fucosyl and xylosyl addition, such as mannosidase II (Man II). See page 69, line 24 to page 70, first full ¶, and Figure 16.

(Office Action at page 6).

As mentioned in Applicants' Amendment and Reply dated February 5, 2008, Russell *et al.* discusses fusion glycosyltransferases in ***plant*** cells and requires the specific

use of early-pathway ***plant*** Golgi localization domains to modify the glycosylation profile of polypeptides. Russell *et al.* does not teach the use of ***mammalian*** host cells expressing a fusion polypeptide comprising (i) GnTIII or GalT activity and (ii) the Golgi localization domain of Man II. As such, Russell *et al.* does not teach, either expressly or inherently, each and every element of the claimed invention.

Further, there is no suggestion or motivation to use a mammalian host cell expressing a fusion polypeptide comprising (i) GnT III or Gal T activity and (ii) the Golgi localization domain of Man II to produce a glycoengineered whole antibody molecule, antibody fragment, or fusion protein that includes a region equivalent to the Fc region of an immunoglobulin simply by combining Umaña *et al.*, Grabenhorst *et al.*, Shields *et al.*, and Russell *et al.* Rather, Russell *et al.* teaches away from using such mammalian host cells by teaching that plant cells are the desired cells for practicing the technology discussed therein. (*See* Russell *et al.* at page 2, lines 25-30). Russell *et al.* states that while "mammalian host cells are capable of correctly folding and glycosylating bioactive proteins, the quality and extent of glycosylation can vary with different culture conditions among the same host cells" and that mammalian host cells "suffer from" numerous "disadvantages." (*See* Russell *et al.* at page 2, line 25 and line 31 through page 3, line 1.) As such, Russell *et al.* in combination with Umana *et al.*, Grabenhorst *et al.*, and Shields *et al.* does not provide a reasonable expectation for successfully generating the particular glycoengineered whole antibody molecules, antibody fragments, or fusion proteins that include a region equivalent to the Fc region of an immunoglobulin produced by the methods of claims 68 and 190.

5. Rabouille et al.

As mentioned in Applicants' specification, Rabouille *et al.* discusses the fine Golgi distributions of GnT I and Man II using quantitative immunoelectron microscopy. *See* specification at page 98, paragraph [0255]. Both GnT I and Man II are localized mainly in the medial and trans-cisterna of the Golgi stack, with higher glycosyltransferase concentrations observed in the ***medial*** region relative to the trans-cisterna. However, Rabouille *et al.* does not discuss the redistribution of glycosyltransferases, much less the redistribution of GnT III or GalT. As such, Rabouille *et al.* does not cure the deficiencies of Umana *et al.*

Further, Rabouille *et al.* in combination with Umaña *et al.,* Grabenhorst *et al.,* Shields *et al.,* and Russell *et al.* does not provide a reasonable expectation for successfully generating the particular glycoengineered whole antibody molecules, antibody fragments, or fusion proteins that include a region equivalent to the Fc region of an immunoglobulin produced by the methods of claims 68 and 190.

Applicants' direct the Examiner's attention to their post-filing data described in Ferrara *et al., Biotech. Bioeng. 93*:851-861 (2006) which illustrates the glycan and FcγRIIIa binding differences observed between anti-CD20 antibodies glycoengineered in:

a) HEK293-EBNA host cells overexpressing rat Gnt III;

b) HEK293-EBNA host cells expressing fusion glycosyltransferases comprising rat GnT III catalytic activity and a human Man II Golgi localization domain; and

c) HEK293-EBNA host cells expressing fusion glycosyltransferases comprising rat GnT III catalytic activity and a human GnT I Golgi localization domain.

Figure 2A and Table I of Ferrara *et al.* show that the use of a GnT I or Man II localization domain in the place of a native GnT III localization domain results in an increased proportion of bisected non-fucosylated hybrid oligosaccharides (mainly *m/z* 1664) linked to the secreted antibody. The overexpression of GnT III in mammalian host cells co-expressing antibodies, on the other hand, led to the production of antibodies with lower levels of bisected non-fucosylated oligosaccharides with lower FcγRIIIa binding affinity as compared to antibodies that had been glycoengineered in host cells co-expressing fusion glycosyltransferases comprising rat GnT III catalytic domains and human Man II Golgi localization domains. *See* Ferrara *et al.* at pages 856-857 and Figure 4. Applicants submit that none of the above-cited references, alone or in combination, teach or suggest such glycan structural differences or such antibody functional differences.

6. Summary

The Examiner asserts that the combination of Umaña *et al.,* Grabenhorst *et al.,* Shields *et al.,* Russell *et al.,* and Rabouille *et al.* renders the invention obvious. As explained above, the claimed invention is non-obvious because the cited references (1) do not teach (individually or in combination) using host cells expressing a fusion polypeptide comprising (i) GnTIII or GalT activity and (ii) the localization domain of ***Man II*** to produce whole antibody molecules, antibody fragments, or fusion proteins that include a region equivalent to the Fc region of an immunoglobulin; (2) do not provide one of skill in the art with a reason to modify the references to arrive at the claimed invention; and (3) do not provide a reasonable expectation of success. As such,

Applicants submit that the Examiner has failed to make a *prima facie* case of obviousness.

Accordingly, it is respectfully requested that the rejection of claims 68 and 190 under 35 U.S.C. § 103, as allegedly obvious, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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